

## Highly variable drugs: reasons for high variability and solutions to overcome BE problems

Prof. Henning H. Blume, PhD DSc  
SocraTec R&D, Oberursel/Germany  
Concepts in Drug Research and Development  
[www.socratec-pharma.de](http://www.socratec-pharma.de), [www.socratec.eu](http://www.socratec.eu)

Modern Strategies for the Development of Generic Drugs  
20<sup>th</sup> AGAH Annual Meeting, Hamburg, February 22, 2010

## A very long story ...

---

### First step: Bio-international '89

- HVD identified as significant BE problem

#### Statement Prof. Lezlie Benet

*"For a drug, not a narrow therapeutic index compound, with significant PK variability in BA tests the statisticians estimated that a crossover study in 162 volunteers would be requested to meet the acceptance criteria to prove bioequivalence. I suggested that such study was inappropriate ..."*

### Milestone: Bio-international '92

- definition of highly variable drugs
- sources of variability

## Highly variable drugs

◆ SoeraTec R&D

### Definition BIO-international '92 [2001]

*"Drugs which exhibit intra-subject variabilities >30 % ( $CV_{ANOVA}$ ) are to be classified as highly variable ..."*

### Essential differentiation

- highly variable drug substances, e.g. statins
- highly variable drug products, e.g. enteric coated

### Sources of (high) variability

- administration conditions, interactions with food
- physiological factors (GE, transit, first-pass, ...)
- technical aspects, e.g. bioanalytical procedures

## ... over more than a decade ...

◆ SoeraTec R&D

### Numerous international conferences

- Bio-international '94, Munich/Germany
- Bio-international '96, Tokyo/Japan
- FDA/AAPS Conference 1998, Montreal/Canada
- 1<sup>st</sup> PSWC, San Francisco/U.S.A.
- EUFEPS Conference 2002, Copenhagen/Denmark
- ...

### Research initiated

- replicate design, assessing within-subject variability
- multiple dosing, significant dampening of variability

## ... waiting for solution(s)



### US-FDA: clear tendency

- in favour of replicate design approach
- rejection of multiple dosing as less discriminative ...

### Individual BE - "a comedy of errors" (Shakespeare) ?

- "prescribability" vs. "interchangeability"
- S\*F interaction – what does it mean therapeutically ?
- concept on trial for two years, then dismissed ...

### Reference scaled procedure – more than a tryout ?

- widening of acceptance criteria due to scaling ...
- ... based on Reference product related variability

## The problem continues



### Market experience

800 studies (s.d., fasted) evaluated in the U.S.A.

WSV	failed studies (%)
< 10 %	6 %
10-20 %	10 %
20-30 %	26 %
>30 %	62 %

number of subjects	failed studies (%)
0-12	79 %
13-18	70 %
19-24	18 %
25-36	20 %
37-48	23 %
49-60	68 %
>60	12 %

M. Tanguay et al.: AAPS Abstract, 2002

## Ultimate rationale: widening



### Based on clinical justification

- the European approach for long time (decades) ...
- ... "deemphasised" due to various concern/difficulties

### Broad support for scaling procedure

- US-FDA intended to implement Guideline
- concept:
  - replicate design BE studies for HVD
  - widening based on reference product variability

... and Europe ?

## Europe takes initiative ...



London, 27 April 2006  
Doc. Ref. EMEA/CHMP/EWP/147231/2006

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE  
(CHMP)

CONCEPT PAPER FOR AN ADDENDUM TO THE NOTE FOR GUIDANCE ON THE  
INVESTIGATION OF BIOAVAILABILITY AND BIOEQUIVALENCE:  
EVALUATION OF BIOEQUIVALENCE OF HIGHLY VARIABLE DRUGS AND DRUG  
PRODUCTS

## Concept paper and its consequences



### Suggested approach: scaled average BE

- recommended study design
- appropriate acceptance range
- recommended statistical procedure
- how to proceed with WSV Test > Reference ?
- handling of outliers

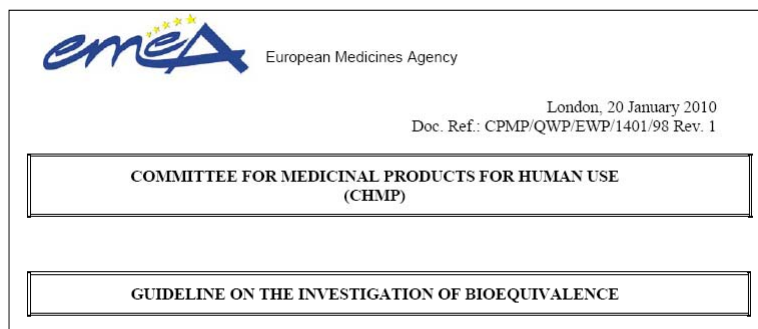
### Paper withdrawn ...

- insurmountable conflictive positions ...
- ... consensus not achievable

## Like Phoenix from the Ashes ...



### New European regulations



#### 4.1.10 Highly variable drugs or drug products

Highly variable drug products (HVDP) are those whose intra-subject variability for a parameter is larger than 30%. If an applicant suspects that a drug product can be considered as highly variable in its rate and/or extent of absorption, a replicate cross-over design study can be carried out.

## Highly variable drugs: European regulations – useful in solving problems in BE assessment ?

Dr. Jan Welink

College ter Beoordeling van Geneesmiddelen (MEB)  
The Hague/The Netherlands

Modern Strategies for the Development of Generic Drugs  
20<sup>th</sup> AGAH Annual Meeting, Hamburg, February 22, 2010